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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,168	12/14/2001	Hsi Liu	6395-61666	9437

7590 08/21/2003

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	10

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	10/017,168	LIU ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,27,28,30 and 31* is/are pending in the application.

4a) Of the above claim(s) *4,8-10 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,11-16,28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other: *Sequence Form* .

DETAILED ACTION

1. Applicant's response to the Restriction requirement filed May 27, 2003 is acknowledged. Applicant's election of Group I with traverse claims 1-16, 27-28 and 30-31 and election of SEQ ID NO:15 is acknowledged. Claims 17-26, 29 and 32-36 have been cancelled. Claims 4, 8-10 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species. Claims 1-3, 5-7, 11-16, 28 and 30-31 are under consideration.

Specification Objections

2. This application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 because it contains amino acid sequences and nucleic acid sequences that are not identified. For example, Figures 5 and 6 contain sequences that are not identified. Although the Brief Description of the Figures gives information about the figures, all sequences listed in for example, Figures 5 and 6 have not been identified by sequence identifiers (SEQ ID Nos) as required to comply with the sequence rules. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application. Applicant is asked to review the specification for these types of informalities. Correction is required. See the attachment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 5-7, 11-16, 28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting the presence of *Treponema pallidum* or anti-treponemal antibodies in a biological sample comprising contacting an isolated immunogenic *Treponema pallidum* peptide of the acid repeat protein (SEQ ID NO:15, elected sequence), does not reasonably provide enablement for conservative variations of SEQ ID NO: 15.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification states that "SEQ ID NO:15 shows the amino acid sequence of a peptide isolated form the acidic repeat protein of *T. pallidum*, Nichols strain". The specification teaches that one of skill in the art will recognize that individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids in an encoded sequence are conservatively modified variations in which the alterations result in the substitution of an amino acid with a chemically similar amino acid (page 16 –17). The specification is <u>not enabling</u> for conservative variations of SEQ ID NO: 15.

The specification fails to teach how to make and use conservative variations of SEQ ID NO: 15. The specification does not disclose the structure of conservative variations of SEQ ID NO: 15.

There is no guidance provided as to which amino acids can be modified and still have the protein retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any

protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such proteins. There is no guidance provided in the specification as how one would begin to make the claimed conservative variations.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that: 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to conservative variations of SEQ ID NO: 15 having the claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level).

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement

(In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986). One of skill in the art would require guidance, in order to make conservative variations of SEQ ID NO: 15 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to practice (make and use) the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 5-7, 11-16, 28 and 30-31 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of the claims is not as precise as the subject matter permits such that one would reasonably know the metes and bounds of the claimed subject matter.

a) Claims 1, 2, 16, 28 and 30 recite "acid repeat protein" it is unclear as to what the applicant is referring? Correction is required.

b) Claims 2 and 30-31 recite "immunogenic repeat region" it is unclear as to what the applicant is referring? Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 5-6, 11-16 and 30-31 are rejected under 35 U.S.C. 102(b) as anticipated by Farshy et al *(Journal of Clinical Microbiology, December 1984, p. 1109-1113)*.

Claims 1-3, 5-6, 11-16 and 30-31 are drawn to a method of detecting the presence of *Treponema pallidum* or anti-treponemal antibodies in a biological sample comprising contacting an acidic repeat protein or one or more isolated immunogenic *Treponema pallidum* peptides of the acidic repeat protein with an antibody-containing biological sample wherein the acid repeat protein or isolated immunogenic *Treponema pallidum* peptide(s) of the acid repeat protein comprises the amino acid sequence $EVEDX_1PX_2VVEPASX_3X_4EGGER$, wherein X_1 is A or V; X_2 is K or G; X_3 is E or G; and X_4 is R or H; and detecting formation of a complex between the immunogenic protein or peptide and the antibody, wherein the presence of the complex indicated the presence of *Treponema pallidum*.

Farshy et al teach a method of detecting the presence of anti-treponemal antibodies in a biological sample by using an enzyme-linked immunoassay (ELISA) for the measurement of immunoglobin G (IgG) and IgM which was developed to detect antibodies to *T. pallidum*. Farshy et al teach that well of polystyrene microtiter plates (solid phase) were coated with *T. pallidum* antigen, diluted patient serum was added and IgG and IgM which bound to the *T. pallidum* antigen were measured by the simultaneous addition of alkaline phosphatase-labeled anti-human IgG and horseradish peroxidase-labeled anti-human IgM (see the Abstract). Farshy et al teach that the results of the study indicate that the ELISA method could prove to be a valuable confirmatory test for syphilis (page 1111, 2nd column). Farshy et al teach that the test is simple, can be read automatically, appears to be sensitive, specific for studying two immunoglobulins as the relate to the diagnosis of syphilis (page 1111, 2nd column). The sequence of the *T. pallidum* peptide, for example SEQ ID NO: 15 would be inherent in the teachings of the prior art. Farshy et al, anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

6. Claims 1-3, 5-6, 11-16 and 30-31 are rejected under 35 U.S.C. 102(b) as anticipated by Hook et al *(Journal of Clinical Microbiology, August 1985, p. 241-244).*

Claims 1-3, 5-6, 11-16 and 30-31 are drawn to a method of detecting the presence of *Treponema pallidum* or anti-treponemal antibodies in a biological sample comprising contacting an acidic repeat protein or one or more isolated immunogenic *Treponema pallidum* peptides of the acidic repeat protein with an antibody-containing biological sample wherein the acid repeat protein or isolated immunogenic *Treponema pallidum* peptide(s) of the acid repeat protein comprises the amino acid sequence $EVEDX_1PX_2VVEPASX_3X_4EGGER$, wherein X_1 is A or V; X_2 is K or G; X_3 is E or G; and X_4 is R or H; and detecting formation of a complex between the immunogenic protein or peptide and the antibody, wherein the presence of the complex indicated the presence of *Treponema pallidum.*

Hook et al teach the presence of *Treponema pallidum* in a biological sample by using a direct fluorescent-antibody technique revealed the presence of *T. pallidum* in 30 of 30 patients with early syphilis (see the Abstract). Hook et al teach that antibody H9-1 was used in this study. Hook et al teach that antibody H9-1 is a pathogen specific monoclonal antibody which recognizes an antigenic determinant present on *T. pallidum* and *T. pertenue* (page 241, 2nd column). Hook et al teach that for direct immunofluorescence testing, an acetone-fixed smear from each patient was incubated with fluorescein-conjugated antibody solution containing Evans blue counterstain for 30 minutes. Hook et al teach that the slides (solid phase) were rinsed with water, dried and mounted. Hook et al teach that the demonstration of *T. pallidum* by using fluorescein-

conjugated monoclonal antibodies is intrinsically specific and is as sensitive as dark-field microscopy for the diagnosis of syphilis (see the Abstract). The sequence of the *T. pallidum* peptide, for example SEQ ID NO: 15 would be inherent in the teachings of the prior art. Hook et al, anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. Claims 1-3, 5-6, 11-16 and 30-31 are rejected under 35 U.S.C. 102(b) as anticipated by Stevens et al *(Journal of Clinical Microbiology, February, 1982, p. 191-195).*

Claims 1-3, 5-6, 11-16 and 30-31 are drawn to a method of detecting the presence of *Treponema pallidum* or anti-treponemal antibodies in a biological sample comprising contacting an acidic repeat protein or one or more isolated immunogenic *Treponema pallidum* peptides of the acidic repeat protein with an antibody-containing biological sample wherein the acid repeat protein or isolated immunogenic *Treponema pallidum* peptide(s) of the acid repeat protein comprises the amino acid sequence $EVEDX_1PX_2VVEPASX_3X_4EGGER$, wherein X_1 is A or V; X_2 is K or G; X_3 is E or G; and X_4 is R or H; and detecting formation of a complex between the immunogenic protein or

peptide and the antibody, wherein the presence of the complex indicated the presence of *Treponema pallidum*.

Stevens et al teach a method of detecting the presence of *Treponema pallidum* in a biological sample by using a solid-phase fluoroimmunoassay (SFTA) for treponemal antibody (see the Abstract). Stevens et al teach that antibody is adsorbed onto cellulose acetate disks (solid phase). Stevens et al teach that a probe containing both the antigen and control disks is inserted into a serum dilution, a buffer rinse, fluoroscein isothiocynate-conjugated goat anti-human immunoglobulin G and a second rinse (see the Abstract). Stevens et al teach that treponemal antibody tests are essential for the diagnosis of syphilis and other treponematoses and Stevens et al teach the development of SFTA which is simple to perform and produces an objective, quantitative result (page 191, 2nd column). The sequence of the *T. pallidum* peptide, for example SEQ ID NO: 15 would be inherent in the teachings of the prior art. Stevens, et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 28 is rejected under 35 U.S.C. 103(a) as unpatentable over Farshy et al *(Journal of Clinical Microbiology, December 1984, p. 1109-1113).*

Claim 28 is drawn to a kit for detecting *T. pallidum* in a biological sample using the method of claim 1, comprising an acidic repeat protein or one or more isolated, immunogenic *Treponema pallidum* peptide of the acidic repeat protein and instructions for carrying out the method of claim 1.

Farshy et al teach a method of detecting the presence of anti-treponemal antibodies in a biological sample by using an enzyme-linked immunoassay (ELISA) for the measurement of immunoglobin G (IgG) and IgM which was developed to detect antibodies to *T. pallidum.* Farshy et al teach that the microtiter plates used in the method of detecting the presence of anti-treponemal antibodies in a biological sample comprise the *T. pallidum* peptide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare the immunoassay comprising the *T. pallidum* peptides used in the method of detecting the presence of anti-treponemal antibodies in a biological sample in the form of a diagnostic kit. It would also be obvious to include instructions for carrying out the claimed method using the diagnostic kit.

9. Claim 28 is rejected under 35 U.S.C. 103(a) as unpatentable over Stevens et al *(Journal of Clinical Microbiology, February, 1982, p. 191-195).*

Claim 28 is drawn to a kit for detecting *T. pallidum* in a biological sample using the method of claim 1, comprising an acidic repeat protein or one or more isolated, immunogenic *Treponema pallidum* peptide of the acidic repeat protein and instructions for carrying out the method of claim 1.

Stevens et al teach a method of detecting the presence of *Treponema pallidum* in a biological sample by using a solid-phase fluoroimmunoassay (SFTA) for treponemal antibody (see the Abstract). Stevens et al teach that the cellulose acetate disks use in the method of detecting the presence of *Treponema pallidum* in a biological sample comprise the *T. pallidum* peptide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare the immunoassay comprising the *T. pallidum* peptides used in the method of detecting the presence of treponemal antibodies in a biological sample in the form of a diagnostic kit. It would also be obvious to include instructions for carrying out the claimed method using the diagnostic kit.

Status of Claims

10. No claims are allowed.

Conclusion

11. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
August 6, 2003

LYNETTE R. F SMITH
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